Journal of Surgical Research **116,** 145–150 (2004)
doi:10.1016/S0022-4804(03)00301-9

# Superior Mesenteric Artery Occlusion Models Shock-Induced Gut Ischemia-Reperfusion[1]

Rosemary A. Kozar, M.D., Ph.D.,[2] John B. Holcomb, M.D.,[3] Heitham T. Hassoun, M.D., Joseph Macaitis, B.S.,[3] Roland DeSoignie, M.A., and Frederick A. Moore, M.D.

*Department of Surgery, University of Texas–Houston, Houston, TX 77030, USA*

Submitted for publication May 15, 2003

***Background.*** **Superior mesenteric artery occlusion (SMAO) is a simple and reproducible model of shock-induced gut ischemia/reperfusion, but some argue that it is not clinically relevant. The purpose of the current study was to compare SMAO to a standard model of controlled hemorrhage (CH) and uncontrolled hemorrhage (UH).**

***Methods.*** **Rats had femoral lines and a jejunal mucosal laser Doppler placed followed by SMAO (60 min of ischemia, no resuscitation), controlled hemorrhage (40 mm Hg for 60 min, 2:1 resuscitation shed blood and lactated Ringers), or uncontrolled hemorrhage (liver injury, 3:1 resuscitation with lactated Ringers). Base deficit, lactate, and jejunal mucosal flow (as a percentage of baseline) were recorded during ischemia and for 120 min after reperfusion. Jejunal tissue was harvested for morphological evaluation. Comparison among groups was by analysis of variance (ANOVA), and significance was set at $P < 0.05$.**

***Results.*** **Mucosal blood flow was similar among groups at the onset of reperfusion (CH, 16.9 ± 5.0% *versus* UH, 10.9 ± 3.1% *versus* SMAO, 13.9 ± 6.2%) and during the initial period of reperfusion. By 120 min, however, flow in CH (75.4 ± 2.5%) was significantly higher that in either UH (36.4 ± 13.1%) or SMAO (31.7 ± 8.4%). Histological injury was less with CH, while base deficit was significantly higher in CH at the onset of reperfusion (−24 ± 2 *versus* UH, −10 ± 3 and SMAO, −6 ± 3 mM/L) but comparable by the end (CH, −17 ± 4 *versus* UH, −16 ± 3 and SMAO, −17 ± 2 mM/L).**

***Conclusion.*** **SMAO is a clinically relevant model of shock-induced gut ischemia/reperfusion.**

***Key Words:*** **rodent model; shock; ischemia/reperfusion; superior mesenteric artery occlusion; uncontrolled hemorrhage; controlled hemorrhage.**

## INTRODUCTION

Gut ischemia/reperfusion (I/R) is thought to be a prime inciting event for post injury multiple organ failure [1, 2]. Clinically, shock has consistently been shown to be a strong predictor of multiple organ failure [3]. In the laboratory, it has been demonstrated that shock causes disproportionate splanchnic vasoconstriction that persists despite adequate systemic resuscitation [4, 5]. This has been verified in the ICU, where persistent gastric mucosal hypoperfusion (documented by tonometry) in patients undergoing shock resuscitation predicts multiple organ failure and death [6, 7]. Finally, it has been convincingly shown that shock-induced gut I/R elaborates mediators that cause remote organ injury [8–10].

The optimal laboratory model to study shock, however, has not been well agreed upon and depends upon the research question being asked. The model of controlled hemorrhage (CH) dates back to the early 1900s, when Carl Wiggers, a physiologist, was studying the phenomenon of irreversible shock [11]. CH was then adopted and adapted (i.e., the modified "Wiggers Prep") by surgeons, the most notable being Shires *et al.* and Moyer *et al.*, to study optimal methods of shock resuscitation [12, 13]. This pioneering work culminated in

Presented at the Annual Meeting of the Association for Academic Surgery, Boston, Massachusetts, November 7–9, 2002.

[1] Supported by grants from the National Institutes of Health NIGMS Grant P50 GM 38529 and K08 GM62975 (RAK)

[2] To whom correspondence and reprint requests should be addressed at Department of Surgery, University of Texas–Houston, 6411 Fannin, M.S.B. 4.284, Houston, TX 77030. E-mail: Rosemary.A.Kozar@uth.tmc.edu.

[3] Current address: United States Army Institute of Surgical Research, Fort Sam Houston, TX. 



0022-4804/04 $30.00

# Report Documentation Page

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| **01 JAN 2004** | **N/A** | **-** |

| 4. TITLE AND SUBTITLE | 5a. CONTRACT NUMBER |
|---|---|
| **Superior mesenteric artery occlusion models shock-induced gut ischemia-reperfusion** | 5b. GRANT NUMBER |
| | 5c. PROGRAM ELEMENT NUMBER |
| 6. AUTHOR(S) | 5d. PROJECT NUMBER |
| **Kozar R. A., Holcomb J. B., Hassoun H. T., Macaitis J., DeSoignie R., Moore F. A.,** | 5e. TASK NUMBER |
| | 5f. WORK UNIT NUMBER |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234** | 8. PERFORMING ORGANIZATION REPORT NUMBER |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | 10. SPONSOR/MONITOR'S ACRONYM(S) |
| | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) |

12. DISTRIBUTION/AVAILABILITY STATEMENT
**Approved for public release, distribution unlimited**

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a REPORT | b ABSTRACT | c THIS PAGE | | | |
| **unclassified** | **unclassified** | **unclassified** | **SAR** | **6** | |

our current standard care of isotonic crystalloid resuscitation (primarily lactated Ringers) and blood at a ratio of 3:1. However, in 1980, Rocha E. Silva and associates published a landmark study in which they demonstrated that small-volume resuscitation with hypertonic saline in CH had remarkably better survival compared to an equal volume of isotonic saline [14]. Subsequent investigators identified that hypertonic saline caused increased bleeding, presumably due to arteriolar vasodilatation, and they developed models of uncontrolled hemorrhage (UH), arguing that CH was not clinically relevant [15, 16]. Unfortunately, these models (tail resection [16], hole punch in aorta [17], splenic laceration [18], and hepatic laceration [19]) are difficult to use due to the variable blood loss, blood pressure, and mortality response to similar anatomical injuries.

Our laboratory is interested in shock-induced gut I/R and its effect on gut inflammation and function. To investigate this, we have used a simple and reproducible model of superior mesenteric artery occlusion (SMAO). However, some reviewers criticize this model as not being clinically relevant. The purpose of the current study, therefore, was to compare systemic perfusion, mucosal perfusion, and mucosal injury in three established models of shock: CH, UH, and SMAO.

## METHODS

Sprague Dawley rats weighing 250–350 grams were used after a period of acclimatization. Rats were fasted overnight but allowed free access to water. Anesthesia was induced and maintained with 2% isoflurane, and body temperature was maintained at 37°C by use of a warming blanket. At the conclusion of the experiment, cardiac puncture and exsanguination were used to achieve euthanasia. All procedures performed were under approved protocols by the Animal Welfare Committee of the University of Texas-Houston School of Medicine.

A polyethylene catheter (PE-50) was introduced into the femoral artery and a 14-gauge angiocatheter into the vein for blood pressure and hemodynamic measurements, blood sampling, and intravenous fluid administration. Mean arterial pressure (MAP) was recorded at 1-min intervals throughout the study period using a continuous data collection system (Micro-Med, Louisville, KY) connected to the arterial line. Blood (250 $\mu$L) was drawn into a heparinized syringe for arterial blood gas analysis (i-STAT, Abbott Laboratories, East Windsor, NJ).

An upper midline laparotomy was performed and the jejunum identified 5 cm distal to the ligament of Treitz. A Teflon-coated laser optic flow probe (Peri flux PF409, flexible probe with 0.25-mm fiber separation) was inserted through a small enterotomy and positioned along the antimesenteric border of the proximal jejunum [20]. Mucosal blood flow was continuously recorded with a laser Doppler flow monitor (Peri Flux 4001 Master; Perimed, Jaarnfalla, Sweden). Measurements were taken as the average flow (in arbitrary perfusion units) [21] over a 5-min period following an initial 30-min period of stabilization and recorded as a percentage of baseline flow. The use of laser Doppler-measured tissue perfusion is a reliable technique that has been validated in the gastrointestinal mucosa [22].

Shock was then introduced by one of three methods ($n$ = 4-6/group): controlled hemorrhage, uncontrolled hemorrhage, or superior mesenteric artery occlusion, and animals were followed throughout 120 min of reperfusion. At the time of sacrifice, full thickness segment of jejunum just proximal to enterotomy for the laser Doppler was harvested for microscopic examination. Sections were stained with hematoxyline and eosin and then examined under a light microscope in a blinded manner (HTH). Mucosal injury was scored on a scale from 0 to 5 as described by Chiu *et al.* [23]. The grading system was as follows: grade 0, normal mucosal villi; grade 1, subepithelial Gruenhagen's space, capillary congestion; grade 2, extension of subepithelial space with moderate lifting of epithelial layer from lamina propria; grade 3, massive epithelial lifting down sides of villa, few tips denuded; grade 4, denuded villi with lamina propria and dilated capillaries exposed; and grade 5, digestion and disintegration of lamina propria, hemorrhage and ulceration.

### Controlled Hemorrhage

Hemorrhagic shock was induced by withdrawing blood from the femoral artery into a heparinized syringe over 10 min to achieve and then maintain a mean arterial pressure (MAP) of 40 mm Hg [24, 25]. Following 60 min of shock, the animals were resuscitated to a MAP of 80 mm Hg by administration of the remaining shed blood plus two times the shed blood volume as lactated Ringers solution. The onset of reperfusion was marked by the reinfusion of blood. Blood samples were obtained at baseline, after 60 min of hemorrhage, and at the end of 120 min of resuscitation.

### Uncontrolled Hemorrhage

The capsule of the median lobe of the liver was scored 1.5 cm from the suprahepatic vena cava, and the portion of the liver distal to the mark was sharply excised. Because of established variability inherent to this model, rats were excluded if the weight of the excised lobe of the liver divided by the baseline total body weight was either less than 0.8% or greater than 1.2% [19]. Five minutes after the onset of hemorrhage, Floseal (4 mL, Fusion Medical Technologies, Mountain View, CA) was applied to the cut surface of the liver to aid in hemostasis. Resuscitation to the baseline MAP with three times the shed blood volume as lactated Ringers solution was begun 5 min after the onset of hemorrhage [17]. Blood gas samples were obtained at baseline, 5, and 120 min after the onset of hemorrhage. Five minutes marked the onset of reperfusion, as resuscitation was instituted at this time. Due to the severity of the insult, longer times of hemorrhage were not tolerated, and a hemostatic agent was required to ensure survival through 120 min of reperfusion.

### Superior Mesenteric Artery Occlusion

The superior mesenteric artery was isolated at its origin and clamped for 60 min [26] followed by reperfusion for 120 min. Blood gas samples were obtained at baseline, at the end of 60 min of ischemia, and after 120 min of reperfusion.

### Statistical Analysis

Comparison among groups was performed using one-way analysis of variance (ANOVA) followed by Tukey's test. Significance was set at $P < 0.05$; data are reported as mean ± SEM.

## RESULTS

### Systemic Perfusion

#### *Mean Arterial Pressure*

MAP was similar for all groups prior to the onset of ischemia (CH, 92 ± 5 mm Hg; UH, 91 ± 3 mm Hg;

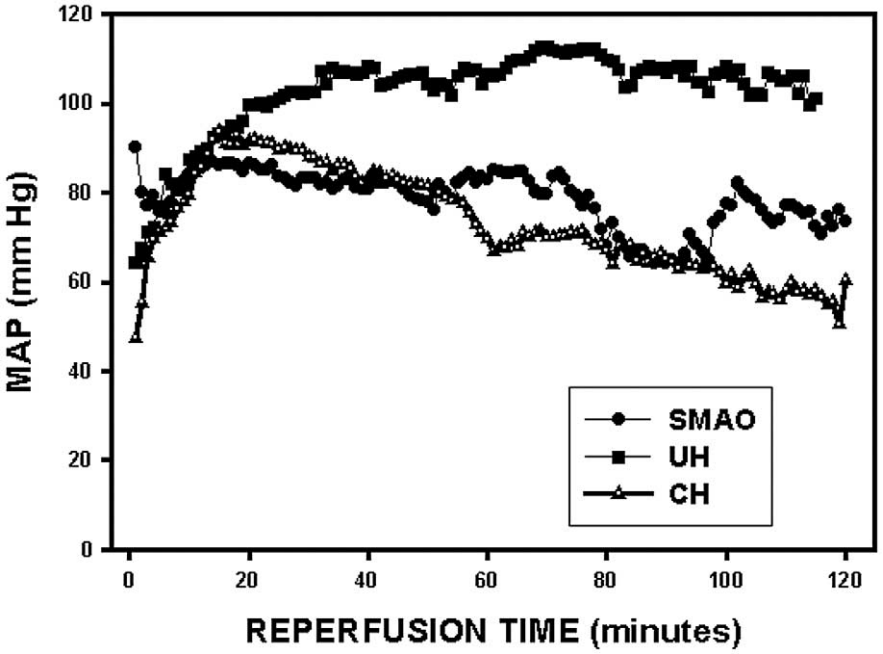


**FIG. 1.** Mean Arterial Pressure (MAP) during reperfusion. The average MAP during each of 120 min of reperfusion is compared among groups ($n$ = 4-6/group). SMAO = superior mesenteric artery occlusion; UH = uncontrolled hemorrhage; CH = controlled hemorrhage.

SMAO, 90 ± 6 mm Hg) but diverged by the end of ischemia/onset of reperfusion, with SMAO (91 ± 7 mm Hg) being significantly higher than CH (39 ± 3 mm Hg) or UH (61 ± 10 mm Hg). MAP data throughout reperfusion is shown in Fig. 1. Within the first 5 min of reperfusion, MAPs converged and remained similar through 20 min of reperfusion (at 20 min: CH, 92 ± 6 mm Hg; UH, 99 ± 4 mm Hg; SMAO, 87 ± 9 mm Hg), but then began to digress for the remaining period of reperfusion. By the end of reperfusion (120 min), MAP was significantly lower in CH (56 ± 9 mm Hg) than UH (101 ± 6 mm Hg) or SMAO (73 ± 16 mm Hg).

*Arterial Blood Gas Determinations*

Arterial blood gas results are shown in Table 1 for each model of shock at baseline, the onset of reperfusion, and the end of reperfusion. In each group, base deficit was increased by the onset of reperfusion and remained elevated throughout reperfusion. However, CH had a significantly higher base deficit at the onset of reperfusion compared to both UH or SMAO. By the end of reperfusion, all groups were comparable.

**Local Gut Perfusion**

Jejunal mucosal blood flow was comparable among groups at the onset of reperfusion (CH, 16.9 ± 5.0%; UH, 10.9 ± 3.1%; SMAO, 13.9 ± 6.2%) and during the initial 30 min of reperfusion (CH, 50.8 ± 8.0%; UH, 43.4 ± 6.2%; SMAO, 41.8 ± 6.3%). CH thereafter began to diverge from UH and SMAO and was significantly higher than SMAO by 90 min (CH, 72.6 ± 12.5%; SMAO, 29.7 ± 10.8%) and higher than both SMAO and UH by 120 min (CH, 75.4 ± 2.5%; UH, 36.4 ± 13.1%; SMAO, 31.7 ± 8.4%) (Fig. 2).

**TABLE 1**

**Arterial Blood Gas Values**

| Parameter | CH | UH | SMAO |
|---|---|---|---|
| Baseline | | | |
| pH | 7.39 ± 0.06 | 7.36 ± 0.02 | 7.37 ± 0.03 |
| $P_{CO_2}$ (mm Hg) | 38 ± 5 | 38 ± 1 | 37 ± 3 |
| $P_{O_2}$ (mm Hg) | 543 ± 28 | 497 ± 13 | 523 ± 27 |
| $HCO_3$ (mM/L) | 23 ± 2 | 22 ± 1 | 22 ± 2 |
| Base excess (mM/L) | 2.3 ± 1.1 | −3.5 ± 1.2 | −3.3 ± 1.9 |
| Onset of reperfusion | | | |
| pH | 7.39 ± 0.06 | 7.27 ± 0.08 | 7.34 ± 0.01 |
| $P_{CO_2}$ (mm Hg) | 38 ± 5 | 29 ± 10 | 38 ± 6 |
| $P_{O_2}$ (mm Hg) | 543 ± 28 | 512 ± 48 | 491 ± 4 |
| $HCO_3$ (mM/L) | 23 ± 2 | 14 ± 7 | 20 ± 3 |
| Base excess (mM/L) | −24.5 ± 2.3[a,b] | −10 ± 3.2 | −5.5 ± 3.0 |
| End of reperfusion | | | |
| pH | 7.39 ± 0.06[b] | 7.31 ± 0.03 | 7.11 ± 0.08 |
| $P_{CO_2}$ (mm Hg) | 38 ± 5 | 22 ± 4 | 39 ± 10 |
| $P_{O_2}$ (mm Hg) | 543 ± 28 | 460 ± 32 | 319 ± 102 |
| $HCO_3$ (mM/L) | 23 ± 2[a] | 11 ± 2 | 13 ± 3 |
| Base excess (mM/L) | −16.8 ± 3.9 | −15.5 ± 2.6 | −16.7 ± 1.6 |

[a] $P < 0.05$ *versus* UH.
[b] $P < 0.05$ *versus* SMAO.

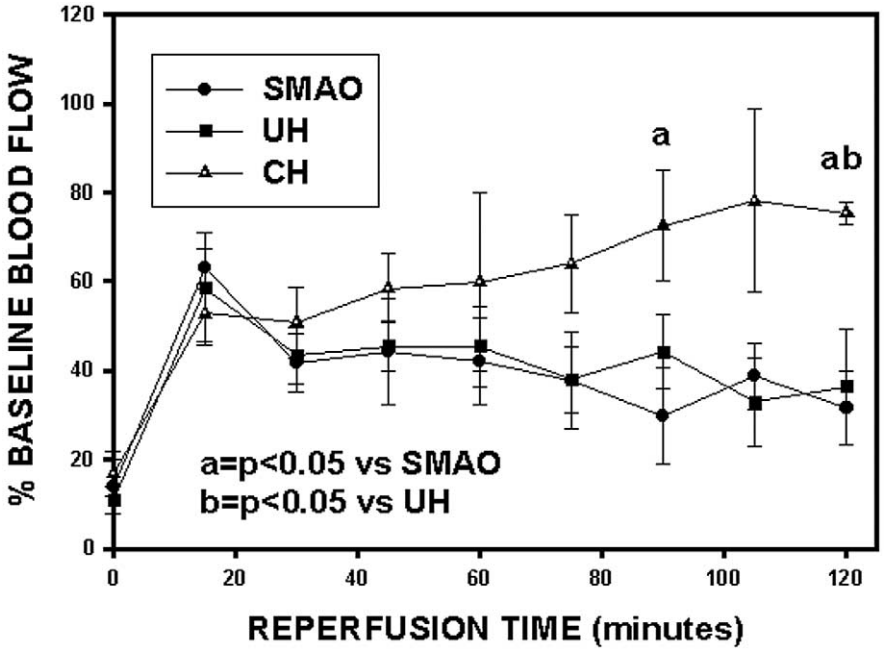


**FIG. 2.** Mucosal blood flow during reperfusion. Results are presented as the percentage of baseline blood flow for each group, mean ± SEM ($n$ = 4–6/group). SMAO = superior mesenteric artery occlusion; UH = uncontrolled hemorrhage; CH = controlled hemorrhage.

### Mucosal Injury

Morphological injury was significantly less in CH compared to UH and roughly correlated with mucosal perfusion at the end of reperfusion (Table 2).

## DISCUSSION

Our laboratory interest is to study the effects of shock on gut inflammation, injury, and dysfunction. The goal of this study was to compare perfusion using three commonly used models of shock to determine which model(s) could mimic the clinical scenario of shock-induced gut I/R. All three models of shock resulted in impairment of both systemic and local gut perfusion. Base deficit increased by the end of ischemia and remained elevated throughout reperfusion. Similarly, gut perfusion remained impaired throughout reperfusion in all models and roughly correlated with the degree of mucosal histological injury. However, CH resulted in a more significant early systemic insult but less of a local gut insult (enhanced perfusion and less mucosal injury) than either UH or SMAO.

**TABLE 2**

**Jejunal Mucosal Injury**

| Shock model | Chiu Score |
|---|---|
| SMAO | 3.7 ± 0.7 |
| Uncontrolled hemorrhage | 4.3 ± 0.3 |
| Controlled hemorrhage | 2.3 ± 0.5[a] |

[a] $P = 0.01$ *versus* uncontrolled hemorrhage.

There are a number of inherent differences among models, including the degree of ischemic insult, the method of resuscitation, and the degree of hemodynamic impairment. First, the duration of ischemia varied among models: in UH, ischemia lasted for approximately 5 min (time when hemostatic agent applied), compared to both CH and SMAO, which used 60 min of ischemia. Because of the variable blood loss and physiological response using uncontrolled hemorrhage, only a brief period of hemorrhage is tolerated. Despite this marked difference in ischemic time, systemic and gut perfusion closely mimicked SMAO. The second difference involved the use and type of resuscitative fluid. CH allows the reinfusion of shed blood plus the use of lactated Ringers as needed to maintain MAP. Because of the difficulty with collecting and then reinfusing blood shed from the peritoneal cavity, only lactated Ringers was infused to maintain MAP with UH. On the other hand, SMAO used no type of fluid resuscitation. Third, the degree and extent of hemodynamic impairment among models differed. CH allows for a carefully maintained MAP during ischemia (40 mm Hg in the current study), whereas MAP is a function of blood loss and autoregulation in UH. With SMAO, there was a brief decrease in MAP with the onset of ischemia, but MAP was otherwise essentially unchanged from baseline. This is in contrast to a recent report by Khanna *et al.* that demonstrated a steep rise in MAP with onset of

ischemia that returned to baseline by the end of ischemia [27]. Similar to the current study, they also found a sustained decrease in MAP with reperfusion, which has been shown to be mediated by the release of platelet activating factor from the postischemic intestine [28–30]. With UH, MAP was increased over baseline throughout most of reperfusion. This may be due to overly aggressive administration of fluid at a time when the animals are hemodynamically unstable coupled with rapid hemorrhage control. Interestingly, despite a high MAP, gut mucosal perfusion remained low throughout reperfusion. CH initially followed a similar pattern, with an initial overshoot of MAP that gradually returned to the target MAP (80 mm Hg). However, after the first 60 min of reperfusion, MAP was persistently decreased. We found that it was difficult to maintain MAP in this group as reperfusion continued. Additional parameters of systemic perfusion, such as oxygen delivery, could provide additional information on the differences in hemodynamic impairment among models. The current study only examined gross indices of perfusion, blood pressure and base deficit, as these parameters are those typically used in the acute management of shock.

The differences in perfusion demonstrated in the current study with CH may be due to the intensity and duration of ischemia and reperfusion chosen, rather than to inherent differences in the model. Other investigators have chosen longer periods of ischemia [31, 32], which may be desirable if the purpose of the experiment is to study gut injury and dysfunction (to increase the extent). However, the greater systemic perturbation exerted by increasing ischemia in this model may also exert a confounding effect on other organs that may then affect the gut. Even with a more significant ischemic insult, (CH 90 min with MAP 35–40 mm Hg), Tisherman *et al.* in a recent study also found gut injury to be minimal [33].

For the perfusion parameters examined, the two models that most closely resembled each other were SMAO and UH, suggesting that these models may be comparable for examining gut function (such as perfusion and injury) following shock-induced gut I/R. Further studies are needed to determine if additional parameters of gut function, such as transit and absorption, are similarly affected. Clearly, uncontrolled hemorrhage is a more clinically relevant model in that it mimics acute, uncontrolled blood loss followed by attempts at hemorrhage control and then fluid resuscitation. This model, however, can be quite variable and more difficult to reproduce [34, 35]. SMAO is simple, highly reproducible, and has been suggested as a useful model for studying intestinal I/R injury [25].

In conclusion, SMAO results in systemic and local gut perfusion comparable to hemorrhagic shock models, particularly uncontrolled hemorrhage. It may therefore be considered as a clinically relevant model of shock-induced gut ischemia/reperfusion.

## REFERENCES


1. Moore, E. E., Moore, F. A., Franciose, R. J., Kim, F. J., Biffl, W. I., and Banerjee, A. Postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. *J. Trauma* **37:** 881, 1997.
2. Hassoun, H. T., Kone, B. C., Mercer, D. W., Moody, F. G., Weisbrodt, N. W., and Moore, F. A. Post-injury multiple organ failure: the role of the gut. *Shock* **15:** 1, 2001.
3. Sauaia, A. J., Moore, F. A., Moore, E. E., Norris, J. M., Lezotte, D. C., and Hamman, R. F. Multiple organ failure can be predicted as early as 12 hours postinjury. *J. Trauma* **45:** 291, 1998.
4. Fiddian–Green, R. G. Hypotension, splanchnic hypoxia and arterial acidosis in ICU patients. *Circ. Shock* **21:** 326, 1987.
5. Reilly, P. M., and Bulkley, G. B. Vasoactive mediators and splanchnic perfusion. *Crit. Care Med.* **21:** S55, 1993.
6. Kirton, O. C., Windsor, J., Wedderburn, R., Hudson–Civetta, J., Shatz, D. V., Mataragas, N. R., and Civetta, J. M. Failure of splanchnic resuscitation in the acutely injured trauma patient correlates with multiple organ system failure and length of stay in the ICU. *Chest* **113:** 1064, 1998.
7. Ivatury, R. R., Simon, R. J., Islam, S., Fueg, A., Rohman, M., and Stahl, W. M. A prospective randomized study of end points of resuscitation after major trauma: Global oxygen transport indices versus organ specific gastric mucosal pH. *J. Am. Coll. Surg.* **183:** 145, 1996.
8. Deitch, E. A., Xu, D., Franko, L., Ayaia, A., and Chaudry, I. H. Evidence favoring the role of the gut as a cytokine-generating organ in rats subjected to hemorrhagic shock. *Shock* **1:** 141, 1994.
9. Tamion, F., Richard, V., Lyoumi, S., Daveau, M., Bonmarchand, G., Leroy, J., Thuillez, C., and Lebreton, J. Gut ischemia and mesenteric synthesis of inflammatory cytokines after hemorrhagic or endotoxic shock. *Am. J. Physiol.* **273:** G314, 1997.
10. Zallen, G., Moore, E. E., Tamura, D. Y., Johnson, J. L., Biffl, W. L., and Silliman, C. C. Hypertonic saline resuscitation abrogates neutrophil priming by mesenteric lymph. *J. Trauma* **48:** 45, 2000.
11. Wiggers, C. J. The present status of the shock problem. *Physiol. Rev.* **22:** 74, 1942.
12. Shires, T., Coln, D., Carrico, J., and Lightfoot, S. Fluid therapy in hemorrhagic shock. *Arch. Surg.* **88:** 688, 1964.
13. Dillon, J., Lynch, L. J., Myers, R., Butcher, H. R., and Moyer, C. A. A bioassay of treatment of hemorrhagic shock. *Arch. Surg.* **93:** 537, 1996.
14. Velasco, I. T., Pontieri, V., Rocha, E., Silva, M., and Lopes, O. U. Hyperosmotic NaCl and severe hemorrhagic shock. *Am. J. Physiol.* **239:** H664, 1980.
15. Gross, D., Landau, E. H., Assalia, A., and Krausz, M. M. Is hypertonic saline resuscitation safe in "uncontrolled" hemorrhagic shock? *J. Trauma* **28:** 751, 1988.
16. Gross, D., Landau, E. H., Klin, B., and Krausz, M. M. Quantitative measurement of bleeding following hypertonic saline therapy in "uncontrolled" hemorrhagic shock. *J. Trauma* **29:** 79, 1989.
17. Burris, D., Rhee, P., Kaufmann, C., Pikoulis, E., Austin, B., Eror, A., DeBraux, S., Guzzi, L., and Leppaniemi, A. Controlled resuscitation for uncontrolled hemorrhagic shock. *J. Trauma* **46:** 216, 1999.
18. Solomonov, E., Hirsh, M., Yahiya, A., and Krausz, M. M. The

effect of vigorous fluid resuscitation in uncontrolled hemorrhagic shock after massive splenic injury. *Crit. Care Med.* **28:** 749, 2000.

19. Holcomb, J. B., McClain, J. M., Pusateri, A. E., Beall, D., Macaitis, J. M., Harris, R. A., MacPhee, M. J., and Hess, J. R. Fibrin sealant foam sprayed directly on liver injuries decreases blood loss in resuscitated rats. *J. Trauma* **49:** 246, 2000.
20. Kozar, R. A., Hu, S., Hassoun, H. T., DeSoignie, R., and Moore, F. A. Specific intraluminal nutrients alter mucosal blood flow during gut ischemia/reperfusion. *JPEN* **26:** 226, 2002.
21. Wang, P., Zhou, M., Cioffi, W. G., Bland, K. I., Zheng, F., and Chaudry, I. H. Is prostacyclin responsible for producing the hyperdynamic response during early sepsis? *Crit. Care Med.* **28:** 1534, 2000.
22. Neviere, R., Chagnon, J. L., Vallet, B., Lebleu, N., Marechal, X., Mathieu, D., Wattel, F., and Dupuis, B. Dobutamine improves gastrointestinal mucosal blood flow in a porcine model of endotoxic shock. *Crit. Care Med.* **25:** 1371, 1997.
23. Chiu, C., McArdle, A. H., Brown, R., Scott, H. J., and Gurd, F. N. Intestinal mucosal lesion in low-flow states. *Arch Surg.* **101:** 478, 1970.
24. Phelan, H., Stahls, P., Hunt, J., Bagby, G. J., and Molina, P. E. Impact of alcohol intoxication hemodynamic, metabolic, and cytokine responses to hemorrhagic shock. *J. Trauma* **53:** 675, 2002.
25. Ba, Z. F., Wang, P., Koo, D. J., Ornan, D. A., Bland, K. I., and Chaudry, I. H. Attenuation of vascular endothelial dysfunction by testosterone receptor blockade after trauma and hemorrhagic shock. *Arch. Surg.* **136:** 1158, 2001.
26. Kozar, R. A., Schultz, S. G., Hassoun, H. T., DeSoignie, R., Weisbrodt, N. W., Haber, M. M., and Moore, F. A. The type of sodium-coupled solute modulates small bowel mucosal injury, transport function and ATP after ischemia/reperfusion injury in rats. *Gastroenterology* **123:** 810, 2002.
27. Khanna, A., Rossman, J. E., Fung, H., and Caty, M. G. Intestinal and hemodynamic impairment following mesenteric ischemia/reperfusion. *J. Surg. Res.* **99:** 114, 2001.
28. Hayward, R., and Lefer, A. M. Time course of endothelial-neutrophil interaction in splanchnic artery ischemia-reperfusion. *Am. J. Physiol.* **275:** H2080, 1998.
29. Mozes, T., Braquet, P., and Filep, J. Platelet-activating factor: An endogenous mediator of mesenteric ischemia-reperfusion-induced shock. *Am. J. Physiol.* **257:** R872, 1989.
30. Filep, J., Braquet, P., and Mozes, T. Significance of platelet-activating factor in mesenteric ischemia-reperfusion. *Lipids* **26:** 1336, 1991.
31. Dayal, S. D., Hauser, C. J., Feketeova, E., Fekete, Z., Adams, J. M., Lu, Q., Xu, D. Z., Zaets, S., and Deitch, E. A. Shock mesenteric lymph-induced rat polymorphonuclear neutrophil activation and endothelial cell injury is mediated by aqueous factors. *J. Trauma* **52:** 1048, 2002.
32. Kuebler, J. F., Jarrar, D., Toth, B., Bland, K. I., Rue, L., Wang, P., and Chaudry, I. H. Estradiol administration improves splanchnic perfusion following trauma-hemorrhage and sepsis. *Arch. Surg.* **137:** 74, 2002.
33. Wu, X., Stezoski, J., Safar, P., Behringer, W., Kentner, R., Kochanek, P. M., and Tisherman, S. A. Systemic hypothermia, but not regional gut hypothermia, improves survival from prolonged hemorrhagic shock. *J. Trauma* **53:** 654, 2002.
34. Tisherman, S. A. Regardless of origin, uncontrolled hemorrhage is uncontrolled hemorrhage. *Crit. Care Med.* **28:** 892, 2000.
35. Deitch, E. A. Animal models of sepsis and shock: A review and lessons learned. *Shock* **9:** 1, 1998.